Attorney Docket No.: 067797-5006-US01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 2359
David A. Horwitz	Examiner: Juedes, Amy E.
Application No.: 10/772,768	Technology Center/Art Unit: 1644
Filed: February 4, 2004	CERTIFICATE OF ELECTRONIC TRANSMISSION
For: METHOD TO PREVENT GRAFT REJECTION USING TGF-BETA TO INDUCE SUPPRESSOR CELLS	I hereby certify that this correspondence, including listed enclosures is being electronically transmitted in Portable Document Form (PDF) through EFS-Web via Hyper Text Transfer Protocol to the United States Patent and Trademark Office's Patent Electronic Business Center on:
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APPELLANT'S BRIEF

Commissioner for Patents
P.O. Box 1450
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Madam:

This Brief is filed in support of Appellant's appeal from the Examiner's Rejection dated April 14, 2008. No claims have been allowed and Claims 1-5 are pending. Claims 1-5 are appealed. A Notice of Appeal was filed on October 14, 2008. As such, this Appeal Brief is timely filed.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

The Commissioner is hereby authorized to charge deposit account number 50-0310, order no. 067797-5006-US01 to cover the fee required under 37 C.F.R. §1.17(c) for filing Appellants' brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0310, order no. 067797-5006-US01

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STATEMENT OF REAL PARTY IN INTEREST

The inventor named on this patent application assigned his entire rights to the invention to University of Southern California.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellant, the undersigned Appellant's representative, or the assignees to whom the inventor assigned her rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF THE CLAIMS

The present application was filed on February 4, 2004 with claims 1-6. During the course of prosecution, Claims 1-5 were amended, and Claim 6 was cancelled. Accordingly, Claims 1-5 are pending in the present application, stand rejected and are appealed herein.

STATUS OF AMENDMENTS

Amendments to the claims were filed August 21, 2006 and February 5, 2008.

SUMMARY OF THE CLAIMED SUBJECT MATTER

Below is a description of each appealed claim and where support for each can be found in the specification.

Independent Claim 1 claims peripheral blood mononuclear cells (PBMCs) comprising one or more suppressor T cells. The PBMCs are capable of decreasing graft rejection of a solid organ by a recipient made by the process comprising isolating peripheral blood mononuclear cells (PBMC) from a recipient and an organ donor, irradiating T cell-depleted mononuclear cells from said organ donor PBMC, and combining ex vivo said recipient PBMC with the donor irradiated T cell-depleted mononuclear cells and a regulatory composition comprising TGF-β to induce one or more recipient suppressor T cells, wherein the suppressor T cells are CD4+CD25+ cells. See original claim 1, and specification example 1.

Independent Claim 2 claims a population of PBMCs comprising suppressor T cells capable of decreasing graft rejection of a solid organ by a recipient. The population of PBMCs is made by a process comprising isolating peripheral blood mononuclear cells (PBMC) from a recipient and an organ donor, irradiating T cell-depleted mononuclear cells from said organ donor PBMC, combining ex vivo said recipient PBMC with said donor irradiated T cell-depleted mononuclear cells and a regulatory composition comprising TGF-β to induce a PBMC population comprising one or recipient suppressor T cells. A recipient suppressor T cell population is produced by expanding the recipient suppressor T cells. The suppressor T cells are CD4+CD25+ cells. See original claim 2, and specification example 1.

Claim 3 depends from claim 1 or 2 wherein the regulatory composition further comprises cytokines selected from the group consisting of IL-2 and IL-15. See original claim 3, and specification example 1.

Claim 4 depends from claim 1 or 2 wherein prior to step (b) the recipient PBMC are enriched for CD4+ T cells. See original claim 4, and specification example 1.

Claim 5 depends from claim 4, wherein the CD4+ cells are enriched for naïve CD4+ T cells. See original claim 5, and specification example 1.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. **The § 102 Rejections of Claims 1-5**

Claims 1-5 are currently rejected under 35 U.S.C. 102(b) as being anticipated by Hall et al. (J. Exp. Med., 1990, 171: 141-157, hereinafter referred to as "Hall").

The Examiner stated in the Office Action mailed April 14, 2008 that:

> Hall et al. teach CD4+ suppressor T cells capable of inhibiting restoration of transplant rejection (i.e. decreasing transplant rejection) (see in particular page 154, Summary, lines 7-8). Additionally, Hall et al. teach CD4+ suppressor T cells to be CD45R (see in particular page 152, 2nd paragraph, line 1) and that CD45R+ cells to be naive cells (i.e. naive CD4+ T cells) (see in particular page 152, 2nd paragraph, lines 14-15). However, Hall et al. do not teach the same process of making the claimed suppressor T cells.

Furthermore, in response to arguments presented in the response to office action filed on February 5, 2008, the Examiner states:

> Applicant's arguments, filed 2/5/08, have been fully considered, but they are not persuasive. Applicant argues that the cells taught by Hall et al. require CD8+ cells to mediate their suppressive effect, while the instant cells exhibit suppressive activity independent of CD8+ cells. As an initial matter, the instant claims are not limited to suppressor T cells that mediate suppression independent of CD8 cells. Additionally, Applicant has not provided any evidence that the cells of the instant claims mediate suppression independent of CD8+ cells. The examples cited by Applicant (Figs. 2A-4B) do not address the suppressive ability of CD4+ T cells in the absence of CD8+ cells. In fact, CD8+ T cells (i.e. CTL) are present in these in vitro assays. Furthermore, Hall et al. demonstrate that suppressor CD4+CD25+ T cells delay graft rejection in the complete absence of CD8+ cells (compare line 1 and line 2 of table V, and see pages 149-150). Therefore, the cells of Hall et al. do mediate some degree of suppression in the absence of CD8 cells. The statement of Hall et al. cited by Applicant (i.e. that a CD8+ cell was critical for transfer of suppression by the the suppressor cells) does not change the fact that the data in Table V demonstrate some degree of suppression of the CD4 cells in the complete absence of CD8 cells.

For this appeal, Appellant focuses on the limitation in Hall that requires the presence of CD8+ cells to make its suppressor cells and the fact that CD8+ cells are

not required to make the suppressor cells as claimed. This difference is evidence that the claimed suppressor cells are different from Hall and therefore patentable.

Appellant seeks to streamline the appeal process by focusing on this limitation, but does not thereby admit to the correctness or appropriateness of any other statement or issue raised by Examiner Juedes.

II. The § 103 Rejections of Claims 1-5

Claims 1-5 are currently rejected under 35 U.S.C. 103(a) as being unpatentable over Groux et al., (Nature, 1997, 289:737-742, hereinafter referred to as "Groux") in view of Seder et al., (J. Immunology, 1998, 160: 5719-5728, hereinafter referred to as "Seder"). The Examiner stated in the Office Action mailed April 14, 2008 that:

> Groux et al. teach a population of regulatory T cells (i.e. suppressor T cells) made by incubating a CD4+ enriched population of PBMC with irradiated allogenic monocytes (i.e. a donor population of mononuclear cells depleted of T cells, see page 739 in particular). Groux et al. also teach that the suppressive activity of the cells is mediated by their production of TGF-β (see page 70 in particular). Groux et al. do not teach incubating the CD4+ T cells with TGF-β. Seder et al. teach that incubating CD4+ T cells with TGF- β enhances the production of TGF-β by the T cells. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to add TGF-β, as taught by Seder et al. to the cultures of regulatory T cells taught by Groux et al. The ordinary artisan at the time the invention was made would have been motivated to do so in order to enhance TGF-β production by the regulatory T cells, since Groux et al. teach that the suppressive activity of the regulatory T cells is mediated by their production of TGF-β, and Seder et al. teach that culture with TGF- β enhances TGF- β production by T cells. Furthermore, claim 5 is included since PBMC enriched for CD4+ cells are enriched for naive CD4+ T cells compared to the starting population of PBMC. Claim 3 is included since the patentability of a product does not depend on its method of production, and Groux et al. and Seder et al. make obvious the suppressor T cells of the instant claims.

Furthermore, in response to arguments provided in a response to office action filed on February 5, 2008, the Examiner states:

> Applicant's arguments, filed 2/5/08, have been fully considered, but they are not persuasive. Applicant argues that the Tr1 cells taught by Seder

> et al. or Groux et al. are not the same as the CD4+CD25+ regulatory cells. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant further argues that neither Groux et al. nor Seder et al. teach combing (*sic*) the starting cells with donor irradiated T-cell depleted mononuclear cells. Groux et al. teach regulatory T cells generated by contacting CD4+ T cells with allogeneic monocytes (i.e. donor Tcell depleted mononuclear cells).

For this appeal, Appellant submits that there is no motivation to combine Groux and Seder, because Groux teaches away from combining Groux and Seder. In addition, Appellant submits that one of skill in the art would have no expectation of success in practicing the claimed invention upon combining the teachings of Groux and Seder, because the cells described by Groux and Seder are not equivalent to the claimed suppressor cells.

Appellant seeks to streamline the appeal process by focusing on these limitations and arguments, but does not thereby admit to the correctness or appropriateness of any other statement or issue raised by Examiner Juedes.

ARGUMENT

Appellant submits that the identical invention is not shown in the references as set forth in the claims. As such, the rejections of claims 1-5 for anticipation under 35 U.S.C. §102 and for obviousness under 35 U.S.C. §103(a) cannot be maintained.

I. REJECTION OF CLAIMS 1-5 UNDER 35 U.S.C. §102: HALL DOES NOT DISCLOSE ALL ELEMENTS OF THE PRESENTLY CLAIMED INVENTION

A. THE CELLS IN HALL ARE NOT IDENTICAL TO THE CLAIMED CELLS

Appellant submits that the cells described in Hall and relied upon by the Examiner are not the same as those of the claimed invention. As a result, Hall does not anticipate the claimed suppressor cells.

The suppressor cells in Hall require the presence of CD8+ cells. Table IV of Hall shows CD4+ suppressor cells can maintain tolerance to a foreign heart graft in adult animals that have been irradiated and thymectomized. Hall speculates that the CD4+ cells may exert suppressive activity by themselves. However, in the data in Table V, Hall clearly shows that radioresistant CD8+ cells are required for the CD4+ suppressor cells to function, and on the next page, Hall explicitly states: "Taken together, these results show the rejection response in irradiated rats is inhibited by an MRC Ox8+ cell that was radioresistant but not thymus derived. This cell was critical for the transfer of suppression by the W3/25+ cells from CSA-treated hosts." emphasis added, Hall, p.148, second full paragraph. (Note that the MRC Ox8+ cells in Hall are CD8+ cells—see page 143 of Hall, first full paragraph). Hall clearly concludes that the CD4+ cells in its system require the presence of CD8+ cells to mediate suppressive activity. However, CD8+ cells are not required for the suppressive activity of the cells of the instantly claimed invention. See pending claims; present application Example 1.

Additionally, the methods disclosed in the instant application have been shown to produce suppressor cells which act independently of CD8+ cells. See Zheng et al., The

Journal of Immunology, 2002, 169: 4183-4189. For example, on page 4186 and in Figure 8, Zheng et al show that CD4+ cells primed with TGF-β develop suppressive activity. Zheng et al do not include CD8+ cells in the experimental systems used to generate the described results, thus supporting Appellant's assertion that the presently claimed invention does not require CD8+ cells, in direct contrast to the system described in Hall.

The Examiner has continued to assert that the cells of Hall mediate some degree of suppression in the absence of CD8+ cells:

> Furthermore, Hall et al. demonstrate that suppressor CD4+CD25+ T cells delay graft rejection in the complete absence of CD8+ cells (compare line 1 and line 2 of table V, and see pages 149-150). Therefore, the cells of Hall et al. do mediate some degree of suppression in the absence of CD8 cells. The statement of Hall et al. cited by Applicant (i.e. that a CD8+ cell was critical for transfer of suppression by the suppressor cells) does not change the fact that the data in Table V demonstrate some degree of suppression of the CD4 cells in the complete absence of CD8 cells. See Office Action dated April 14, 2008, p. 3.

As discussed by David A Horwitz, M.D., in a declaration filed June 11, 2007, this assertion by the Examiner is incorrect: "In Table V, Hall clearly shows that radioresistant CD8+ cells are required for the CD4+ suppressor cells to function. . . . The W3/25+ cells of Hall are CD4+ cells, and the MRC Ox8+ cells are CD8+ cells. Therefore, Hall clearly concludes that the CD4+ cells in its system require the presence of CD8+ cells to mediate suppressive activity. This is not true for the claimed CD4+ suppressor cells." See paragraph 4 of declaration of David A Horwitz, M.D.

The Examiner has also continued to assert that, "Applicant has not provided any evidence that the cells of the instant claims mediate suppression independent of CD8+ cells. The examples cited by Applicant (Figs. 2A-4B) do not address the suppressive ability of CD4+ T cells in the absence of CD8+ cells. In fact, CD8+ T cells (i.e. CTL) are present in these in vitro assays." See Office Action dated April 14, 2008, page 3 lines 1-7. Appellant submits that this assertion by the Examiner is incorrect. Appellant notes that although the claimed processes *can* induce CD8+ cells to exhibit suppressor

activity, the presence of CD8+ T cells is not *required* for the suppressor activity exhibited by the claimed suppressor cells. See currently pending claims 1 and 2. Furthermore, as disclosed in Example 1 of the application, CD4+ cells were isolated from the recipient and activated with TGF-β. CD8+ cells were not present in the system during the process of generating suppressor cells from these isolated CD4+ cells. Figures 2A through 4B show that the T cells generated using the disclosed process are able to block the ability of the recipient's T cells to kill donor cells, even without the presence of CD8+ cells. Although data from CD8+ cells are included in some of the figures, such as in the right-most panel in Figure 2, the experimental systems were separate for the CD4+ and CD8+ systems – i.e., different graphs represent different experimental systems. Thus, the Examiner's contention that Appellant has not shown that the claimed cells mediate suppression independent of CD8+ cells is incorrect.

As the instantly claimed cells do not require the presence of CD8+ cells to have suppressive activity but the cells in Hall do require the presence of CD8+ cells to show suppressive activity, the cells in Hall cannot be identical to those of the instantly claimed invention, and a rejection on these grounds cannot be sustained.

B. THE METHODS OF HALL AND THE METHODS DISCLOSED IN THE INSTANT APPLICATION PRODUCE TWO DIFFERENT POPULATIONS OF CELLS

There is evidence in the literature that the method by which a suppressor cell is generated can affect the nature of that suppressor cell, and that different methods can produce different populations of suppressor cells. The methods used in Hall are different than those used to make the claimed cells. As a result, the cells of Hall are different than those of the present invention, and Hall cannot be used to sustain an anticipation rejection.

Hall uses T cells from cyclosporine-treated animals to produce suppressor T cells. The use of cyclosporine compromises the ability of cells to express Foxp3, a transcription factor that is critical for the differentiation of T cells. See Abstract of

Koenen et al., Bone Marrow Transplant, 2007. It is well known that cyclosporine is typically administered after transplantation to inhibit rejection of the organ.

In the claims, a regulatory composition comprising TGF-β is used to induce the formation of suppressor T cells. The TGF-β induces suppressor cells to express Foxp3, which is in direct contrast to the inhibition of Foxp3 expression seen in cells treated by the methods described in Hall. See Abstract, Zhang et al., J. Cell. Physiol., 2007, 211(3). Foxp3 is a transcription factor that is critical for the differentiation of T cells. In fact, Foxp3 is constitutively expressed by Tregs, controls their differentiation, and is considered a specific marker for Tregs. See page 30 of Roncarolo et al., Immunological Reviews, (2006), 212: 28-50. In addition several investigators have demonstrated that Tr1 cells do not constitutively express Foxp3. See page 30 of Roncarolo et al., Immunological Reviews, (2006), 212: 28-50. As a result, the cells of the current invention, which are CD8+CD28+Foxp3+, are clearly distinguishable from the cells of Hall. See Declaration of David A. Horwitz, M.D., dated June 11, 2007, paragraph 7.

Appellant submits that the methods of Hall and the methods disclosed in the instant application produce two different populations of cells; therefore, Hall cannot support an anticipation rejection.

II. REJECTION OF CLAIMS 1-5 UNDER 35 U.S.C. §103: THERE IS NO MOTIVATION TO COMBINE GROUX AND SEDER, NOR WOULD ONE OF SKILL IN THE ART HAVE A REASONABLE EXPECTATION OF SUCCESS UPON COMBINING THE TEACHINGS OF GROUX AND SEDER

The teachings of Groux are not properly combined with the teachings of Seder to provide the claimed invention. Appellant submits that one of skill in the art would have no motivation to combine the teachings of these references to obtain the claimed invention. In addition, one of skill in the art would have no expectation of success in practicing the claimed invention upon combining the teachings of Groux and Seder.

A. GROUX TEACHES AWAY FROM THE METHOD USED IN SEDER

The disclosure in Groux teaches away from the method used in Seder. As the Board will appreciate, it is improper to combine references where the references teach away from their combination. MPEP § 2145(D)(2); In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir.1983).

Groux teaches that proliferation of the Tr1 clones is augmented by a neutralizing anti-TGF-β monoclonal antibody. See Groux, p. 739, col. 1, lines 1-11. The anti-TGF-β antibody is used to decrease or limit any effect TGF- β would have on the Tr1 clones, and Groux discloses that blocking TGF-β activity using the anti-TGF-β monoclonal antibody augments proliferation of these cells. This teaching in Groux teaches away from combining its disclosed methods with any methods that use TGF-β to produce suppressor cells, because according to the teachings in Groux, adding TGF-β would inhibit the production of suppressor cells. However, the Examiner cites Seder specifically for its teaching that the addition of TGF-β enhances the production of TGF-β by the T cells. The Examiner has equated the cells with increased TGF-β production with the claimed suppressor cells. See office action dated April 14, 2008, page 3, paragraph 6. One of skill in the art would not be motivated to combine Groux with Seder, because Groux teaches that the TGF-β of Seder would work against the goal of inducing and enhancing the proliferation of the Tr1 clones. As such, a rejection for obviousness based on the combination of Groux and Seder cannot be maintained.

The Examiner states that one motivation for combining Groux and Seder is that Groux teaches that "suppressive activity of the regulatory T cells is mediated by their production of TGF-β". See paragraph 6, page 3 of office action dated April 14, 2008. Appellant notes that Groux's description of the mediation of suppressive activity by TGF-β refers to the inhibition of proliferation of the Tr1 cells, which is opposite to the goal of creating the claimed suppressor cells. See Groux, page 740, first full paragraph. Another statement by Groux regarding the mediation of suppressive activity by TGF-β refers to cells that are not the Tr1 cells that are discussed in the remainder of Groux: "These inhibitory activities were relieved by anti-TGF-β, suggesting that these

clones mediated their suppression through TGF-β. Although these T-cell clones appear to have similar functions to Tr1 cells, their cytokine production profiles are different." Emphasis added, see Groux, page 740, third paragraph. Since it is the Tr1 cells in Groux that the Examiner has equated to the claimed suppressor cells, this description of mediation of suppression through TGF-β by cells that are not Tr1 cells cannot provide motivation to one of skill in the art to use the methods of Groux for expanding Tr1 cells in combination with the teachings of Seder. As such, Appellant maintains that Groux teaches away from methods utilizing TGF-β to produce the claimed suppressor cells. One of skill in the art would therefore have no motivation to combine the teachings of Groux with the teachings in Seder regarding the use of TGF-β to produce the claimed suppressor cells. In addition, based on the teachings of Groux, one of skill in the art would also have no expectation that using the TGF-β described in Seder with the methods of Groux would produce the claimed suppressor cells, because Groux clearly states that TGF-β inhibits proliferation of the cells that the Examiner has equated to the claimed suppressor cells.

B. THE CELLS IN GROUX AND SEDER ARE NOT THE CELLS OF THE INSTANTLY CLAIMED INVENTION

The cells in Groux are Tr1 cells, which are made by treating CD4+ enriched PBMC with allogenic irradiated monocytes and IL-10. The Tr1 cells in Groux are activated by IL-10 and in turn produce high levels of IL-10. *See Groux, Abstract.* Such Tr1 cells have a very short life span and limited proliferation potential, as is described in the instant application. See paragraph [0020] of the published application and page 4, lines 7-16 of the application as filed. In contrast, the claimed suppressor cells are CD4+CD25+ regulatory cells (see Fig. 6 of the instant application), which are known in the art to be a different subset of T cells from the Tr1 cells of Groux. See pages 28-29 of Roncarolo et al., Immunological Reviews, 2006, 212: 28-50, which states that Tr1 cells are not the same as the claimed CD4+CD25+ suppressor cells. For example, in the Introduction, Roncarolo makes the following statement:

> The two most relevant classes of Tregs described within the CD4+ subset are T regulatory type 1 (Tr1) cells...and CD4+CD25+ Tregs. These two Treg subsets differ in a number of important biological features, including their specific cytokine secretion profile, cellular markers, ability to differentiate in response to antigen-specific stimuli, and dependency on cytokines vs. cell-cell contact mechanisms for mediating suppressive activity.... Roncarolo, pp. 28-29.

This disclosure in Roncarolo thus shows that the Tr1 cells in Groux are clearly a subset of Tregs that are distinct from the claimed suppressor cells.

The Examiner states that Seder teaches that incubating CD4+ T cells with TGF-β enhances the production of TGF-β by the T cells, and equates these T cells in Seder with the claimed suppressor cells. See office action dated April 14, 2008, page 3, paragraph 6. However, again, there is no indication in Seder that its methods produce the presently claimed suppressor cells. In fact, Seder teaches priming CD4+ T cells with IL-10 before the application of TGF-β. See Seder, page 5722. Again, Roncarolo teaches that "Tr1 cells can be generated *in vitro* and *in vivo* upon priming of naïve T cells with antigen in the presence of IL-10. See Roncarolo, page 29, right column, first full paragraph. As discussed above, Tr1 cells are not equivalent to the claimed suppressor cells.

Based on the above, Appellant submits that neither Groux nor Seder discloses the claimed suppressor cells. As a result, one of skill in the art would have no motivation to combine the teachings of these references to practice the claimed invention, because the combination of Groux and Seder can not provide the claimed suppressor cells. In addition, one of skill in the art would have no expectation of success in practicing the claimed invention upon combining the teachings of Groux and Seder, because neither reference teaches the claimed suppressor cells, and thus together, the teachings of the references still cannot provide the claimed suppressor cells.

The Examiner has stated that "In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references." See Office

Action dated April 14, 2008, page 4. Appellant notes that arguments against each reference must at least in part be provided individually in order to identify which elements of the claimed invention are not covered by the references. Appellant has submitted the above arguments to show that neither Groux nor Seder recites every element of the invention as currently claimed. The discrepancies between Groux and Seder and the present invention are such that even when combined, the two references do not provide all elements of the claimed invention. As the Board will appreciate, the differences between the claimed invention and the prior art must be ascertained. See MPEP § 2141(II). Here, the differences between the invention as currently claimed and Groux are clear, and cannot be rectified by Seder. In addition, as addressed above, there is no motivation to combine Seder with Groux to rectify the deficiencies of Groux. As a result, a finding of obviousness cannot be sustained.

RELIEF REQUESTED

The Appellant respectfully requests that the rejections of Claims 1-5 be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: February 12, 2009

By: _____
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CLAIMS APPENDIX

1. Peripheral blood mononuclear cells (PBMC) comprising one or more suppressor T cells capable of decreasing graft rejection of a solid organ by a recipient made by the process comprising:

a) isolating peripheral blood mononuclear cells (PBMC) from a recipient and an organ donor;

b) irradiating T cell-depleted mononuclear cells from said organ donor PBMC; and

c) combining ex vivo said recipient PBMC with said donor irradiated T cell-depleted mononuclear cells and a regulatory composition comprising TGF-β to induce one or more recipient suppressor T cells, wherein said suppressor T cells are CD4+CD25+ cells.

2. A population of peripheral blood mononuclear cells (PBMC) comprising suppressor T cells capable of decreasing graft rejection of a solid organ by a recipient made by the process comprising:

a) isolating peripheral blood mononuclear cells (PBMC) from a recipient and an organ donor;

b) irradiating T cell-depleted mononuclear cells from said organ donor PBMC;

c) combining ex vivo said recipient PBMC with said donor irradiated T cell-depleted mononuclear cells and a regulatory composition comprising TGF-β to induce a PBMC population comprising one or recipient suppressor T cells; and

d) wherein a recipient suppressor T cell population is produced by expanding said recipient suppressor Tcells. and wherein said suppressor T cells are CD4+CD25+ cells.

3. The PBMC comprising suppressor T cells according to Claim 1 or 2, wherein said regulatory composition further comprises cytokines selected from the group consisting of IL-2 and IL-15.

4. The PBMC comprising suppressor T cells according to Claim 1 or 2, wherein prior to step (b) said recipient PBMC are enriched for CD4+ T cells.

5. The PBMC comprising suppressor T cells according to Claim 4, wherein said CD4+ cells are enriched for naive CD4+ T cells.

EVIDENCE APPENDIX

The following evidence that qualifies under this heading has been submitted during the prosecution of this application and has been referred to in this Appellants' Brief:

Exhibit A: Hall et al., *Journal of Experimental Medicine*, (1990), 171: 141-157, cited in Office Action mailed February 28, 2006, Final Office Action mailed October 10, 2006, Office Action mailed August 6, 2007, and Final Office Action mailed April 14, 2008.

Exhibit B: Groux et al., *Nature*, (1997), 289:737-742, cited in Office Action mailed August 6, 2007, and Final Office Action mailed April 14, 2008.

Exhibit C: Seder et al., *Journal of Immunology*, (1998), 160: 5719-5728, cited in Office Action mailed August 6, 2007, and Final Office Action mailed April 14, 2008.

Exhibit D: Zheng et al., *The Journal of Immunology*, (2002), 169: 4183-4189, submitted by Appellant with Request for Continued Examination (RCE) dated June 11, 2007 as Exhibit 4 in response to Advisory Action mailed April 17, 2007.

Exhibit E: Declaration of David Horwitz, M.D. under 37 C.F.R. §1.132, submitted by Appellant with Request for Continued Examination (RCE) dated June 11, 2007 as Exhibit 4 in response to Advisory Action mailed April 17, 2007.

Exhibit F: Koenen et al., *Bone Marrow Transplant,* (2007), Epub Abstract PMID: 17351648, submitted by Appellant with Request for Continued Examination (RCE) dated June 11, 2007 as Exhibit 6 in response to Advisory Action mailed April 17, 2007.

Exhibit G: Zhang et al., *Journal of Cell Physiology,* (2007), submitted by Appellant with Request for Continued Examination (RCE) dated June 11, 2007 as Exhibit 5 in response to Advisory Action mailed April 17, 2007.

Exhibit H: Roncarolo et al., *Immunological Reviews*, (2006), 212: 28-50, submitted by Appellant in an Amendment dated February 5, 2008 as Exhibit A in response to an Office Action mailed August 6, 2007.

RELATED PROCEEDINGS APPENDIX

As stated in the *Related Appeals and Interferences* section above, there are no other appeals or interferences known to Appellant, the undersigned Appellant's representative, or the assignee to whom the inventor assigned his rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal. As such this section is left blank.

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